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21971	7590	10/26/2006	EXAMINER	
WILSON SONSINI GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 94304-1050			GODDARD, LAURA B	
			ART UNIT	PAPER NUMBER
			1642	

DATE MAILED: 10/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/686,047

Applicant(s)

RUBINFELD ET AL.

Examiner

Laura B. Goddard, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/27/06, 1/25/06, 8/25/05, 1/30/04, 10/17/03
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The Election filed July 27, 2006 in response to the Office Action of June 28, 2006 is acknowledged. Applicant elected the species "interleukin" and "hematological disorder".

Claims 1-25 are pending. Claims drawn to the elected species "interleukin" and "hematological disorder" include 1-4, 8-10, 15-25. Upon review and reconsideration **claims drawn to cytokines (claims 6-12) are rejoined**. Upon review and reconsideration **claims 5, 13, and 14 drawn to cancer diseases are rejoined for examination**. Claims 1-25 are currently under prosecution.

Specification

2. The disclosure is objected to because of the following informalities: There appears to be a grammatical error in section [0041], page 13, where it states: "By reducing hypermethylation, these agents cancer render more effective anti-neoplastic agents". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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3. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a method for treating a disease associated with abnormal cell proliferation or abnormal angiogenesis comprising administering to a patient having the disease a therapeutically effective amount of **an immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation** (claims 1-5, 13-15, 17-23), wherein the immuno-modulating agent is a cytokine (claim 6), wherein the cytokine is selected from the group consisting of erythropoietin, granulocyte-CSF, and granulocyte macrophage-CSF (claim 7), wherein the immuno-modulating agent is interleukin (claim 8), wherein the interleukin is IL-2, IL-4, or IL-12 (claims 9), wherein the interleukin is IL-12 (claims 10 and 16), wherein the immuno-modulating agent is an interferon (claim 11), wherein the interferon is selected from the group consisting of interferon α , interferon β , and interferon γ (claim 12), a kit for treating a disease associated with abnormal cell proliferation comprising a container that contains decitabine and **an immuno-modulating agent** (claim 24), wherein the immuno-modulating agent is interleukin-12 (claim 25).

The specification discloses the agents **cisplatin** and **retinoid** whose activity is adversely affected by aberrant methylation, or hypermethylation ([0044]; [[0047-0048]]).

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The specification discloses non-limiting examples of immuno-modulating agents such as cytokines (interleukins, interferons, erythropoietin, granulocyte-CSF, granulocyte, macrophage-CSF), bacillus Calmette-Guerin, levamisole, and octreotide ([0072-0076]).

The specification does not disclose any immuno-modulating agents whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation.

The specification discloses only **cisplatin** and **retinoid** whose activity is adversely affected by aberrant methylation, or hypermethylation. The specification does not disclose any cytokines whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of “immunomodulating agent” or “immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation”.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-

Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that “ [a] written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name’, of the claimed subject matter sufficient to distinguish it from other materials. ” Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA” without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that “naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.” Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. “A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling

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within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.” Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that “the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an immunomodulating agent or immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by abberant DNA methylation, per Lilly by structurally describing representative immunomodulating agents or immuno-modulating agents whose activity as an immuno-modulating agent in vivo is adversely affected by abberant DNA methylation or by describing “structural features common to the

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members of the genus, which features constitute a substantial portion of the genus.”

Alternatively, per Enzo, the specification can show that the claimed invention is complete “by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.”

In this case, the specification does not directly describe an immunomodulating agent or immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses **retinoid and cisplatin** whose activity is adversely affected by aberrant methylation, or hypermethylation and the specification discloses non-limiting examples of immuno-modulating agents, this does not provide a description of the broadly claimed immunomodulating agents or immuno-modulating agents whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe immunomodulating agents or immuno-modulating agents whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation by the test set out in Lilly because the specification describes only **retinoid and cisplatin** whose activity is adversely affected by aberrant methylation, or hypermethylation and the specification describes non-

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limiting examples of immuno-modulating agents. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of an immunomodulating agent or immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed method uses, it also fails to adequately describe the method.

4. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method for treating leukemia comprising administering to a patient having leukemia a therapeutically effective amount of decitabine and an immuno-modulating agent selected from the group consisting of IL-12, IFN- α , and pyran copolymer or a method for treating melanoma comprising administering to a patient having melanoma a therapeutically effective amount of decitabine and immuno-modulating agent IL-12**, does not reasonably provide enablement for a method for treating a disease associated with abnormal cell proliferation or abnormal angiogenesis comprising administering to a patient having the disease a therapeutically effective amount of an immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation. The specification does not enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for treating **a disease associated with abnormal cell proliferation or abnormal angiogenesis** comprising administering to a patient having the disease a therapeutically effective amount of **an immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation** (claims 1, 23), wherein the DNA

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methylation inhibitor is a **cytidine analog** (claim 2), wherein the cytidine analog is decitabine (claims 3, 16, 18-22), wherein the disease associated with the abnormal cell proliferation is a **hematological disorder** (claims 4, 15), wherein the disease is **renal cell** or malignant melanoma (claim 5), wherein the immuno-modulating agent is a **cytokine** (claim 6), wherein the cytokine is selected from the group consisting of **erythroprotrein, granulocyte-CSF, and granulocyte macrophage-CSF** (claim 7), wherein the immuno-modulating agent is **interleukin** (claim 8), wherein the interleukin is IL-2, IL-4, or IL-12 (claims 9), wherein the interleukin is IL-12 (claims 10 and 16), wherein the immuno-modulating agent is an **interferon** (claim 11), wherein the interferon is selected from the group consisting of interferon α , interferon β , and interferon γ (claim 12), the method according to claim 4 wherein the **benign tumor** is selected from the group consisting of **hemangiomas, hepatocellular adenoma...pyogenic granulomas** (claim 13), wherein the cancer is selected from the group consisting of **breast cancer, skin cancer, bone cancer...epidermoid carcinomas** (claim 14), a kit for treating a **disease associated with abnormal cell proliferation** comprising a container that contains decitabine and an **immuno-modulating agent** (claim 24), wherein the immuno-modulating agent is interleukin-12 (claim 25).

The claims are broadly drawn to a method for treating **any disease associated with abnormal cell proliferation or any abnormal angiogenesis** comprising administering to a patient **any DNA methylation inhibitor** in combination with **any immuno-modulating agent or any cytokine**, wherein the **immuno-modulating**

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agent's activity is adversely affected by aberrant DNA methylation, wherein the disease is any hemological disorder, renal cell carcinoma, various benign tumors in claim 13, and a list of cancers in claim 14.

The specification discloses the inhibitor of DNA methylation decitabine, 5-aza-2'deoxyctodine (p. 12, [0037-0041]). The specification discloses the agents cisplatin and retinoid whose activity is adversely affected by aberrant methylation, or hypermethylation ([0044]; [[0047-0048]]). The specification discloses non-limiting examples of immuno-modulating agents such as cytokines (interleukins, interferons, erythropoietin, granulocyte-CSF, granulocyte, macrophage-CSF), bacillus Calmette-Guerin, levamisole, and octreotide ([0072-0076]).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide examples or guidance for treating **any disease** associated with abnormal cell proliferation or abnormal angiogenesis comprising administering to a patient **any DNA methylation inhibitor** in combination with **any immuno-modulating agent**. The specification does not provide a nexus between the treatment of any disease associated with abnormal cell proliferation or abnormal angiogenesis and administering any DNA methylation inhibitor in combination with any immuno-modulating agent.

In the art, Zaharko et al (Cancer Treatment Reports, 1984, 68:1255-1264), teach a method for treating leukemia comprising administering decitabine (also known as 5-aza-2'deoxyctidine or DAC) and the immuno-modulating agent pyran copolymer (abstract; page 1255, col. 2; p. 1256, col. 1; Fig. 5). Kantarjian et al (Clinical Cancer

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Research, 1997, 3:2723-2733) teach a method for treating chronic myelogenous leukemia comprising administering decitabine and the cytokine interferon- α (abstract; p. 2727, col. 2 and p. 2728, col. 1). Kozar et al (Clinical Cancer Research, 2003, 9:3124-3133, IDS) teach treating melanoma or leukemia comprising administering decitabine and interleukin-12 (abstract; p. 3125, col. 1). Kozar et al teach that although they demonstrated the induction of an immune response both in mice bearing leukemia and melanoma, the overall therapeutic effect of the combined treatment seems to be tumor type-dependent and that it is not clear why the combination of IL-12 and decitabine is more effective against L1210 leukemia than against B16F10 melanoma (p. 3131, col. 2). There are specific combinations of IL-12 and chemotherapeutics that are effective in some but not in other tumor models (p. 3131, col. 2 to p. 3132, col. 1). The art provides examples and is enabling for a method for treating leukemia comprising administering to a patient having leukemia a therapeutically effective amount of decitabine and an immuno-modulating agent selected from the group consisting of IL-12, IFN- α , and pyran copolymer or a method for treating melanoma comprising administering to a patient having melanoma a therapeutically effective amount of decitabine and immuno-modulating agent IL-12. With regards to treating any other diseases associated with abnormal cell proliferation or abnormal angiogenesis or other hematological diseases comprising administering any other DNA methylation inhibitor and any other immuno-modulating agent or cytokine, the specification does not provide any enabling examples. The art teaches the unpredictability of treating any tumor type using a combination of decitabine and IL-12. Given the lack of guidance in the specification and teaching of the

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art, one of skill in the art could not predictably treat any disease associated with abnormal cell proliferation or abnormal angiogenesis and administering any DNA methylation inhibitor in combination with any immuno-modulating agent.

Further, the specification does not disclose any immuno-modulating agents **whose activity is adversely affected by aberrant DNA methylation**. The specification discloses the agents cisplatin and retinoid whose activity is adversely affected by aberrant **hypermethylation** ([0044]; [0047-0048]), however, cisplatin and retinoid are not considered immuno-modulating agents by those skilled in the art and were not described as immuno-modulating agents in the specification. Hence it is unclear what immuno-modulating agents would have activity adversely affected by aberrant DNA methylation, since the immuno-modulating agents disclosed in the specification are not described as having the claimed activity adversely affected by aberrant DNA methylation. Given the lack of guidance and examples in the specification and the art, one of skill in the art would not know how to predictably make or use an immuno-modulating agent whose activity in vivo is adversely affected by aberrant DNA methylation in the claimed method.

Therefore, in view of the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4, 6, 11, 12, 15, 17, 18, 19, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Kantarjian et al (Clinical Cancer Research, 1997, 3:2723-2733).

The claims are drawn to a method for treating a disease associated with abnormal cell proliferation or abnormal angiogenesis comprising administering to a patient having the disease a therapeutically effective amount of an immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation (claim 1), wherein the DNA methylation inhibitor is a cytidine analog (claim 2), wherein the cytidine analog is decitabine (claims 3, 16, 18-22), wherein the disease associated with the abnormal cell proliferation is a hematological disorder (claim 4), wherein the immuno-modulating agent is a cytokine (claim 6), wherein the immuno-modulating agent is an interferon (claim 11), wherein the interferon is interferon α (claim 12), wherein the hematological disorder is chronic myelogenous leukemia (claim 15), wherein the decitabine inhibitor is administered intravenously (claims 17, 18), wherein the decitabine is administered to the patient intravenously at a dose ranging from 1 to 100 mg/m² per day (claim 19), and a kit for treating a disease associated with abnormal cell proliferation comprising a container that contains decitabine and an immuno-modulating agent (claim 24).

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Kantarjian et al teach a method for treating chronic myelogenous leukemia comprising administering decitabine in combination with the cytokine interferon- α (abstract; p. 2727, col. 2 and p. 2728, col. 1), wherein the decitabine is administered intravenously to the patient at a dose of 100 mg/m² per day (p. 2727, col. 2). Kantarjian et al teach the contents of the claimed kit: decitabine and an immuno-modulator, interferon- α . All of the limitations of the claims are met.

5. Claims 1-4, 17, 18, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Zaharko et al (Cancer Treatment Reports, 1984, 68:1255-1256).

The claims are drawn to a method for treating a disease associated with abnormal cell proliferation or abnormal angiogenesis comprising administering to a patient having the disease a therapeutically effective amount of an immuno-modulating agent whose activity as an immuno-modulating agent in vivo is adversely affected by aberrant DNA methylation (claim 1), wherein the DNA methylation inhibitor is a cytidine analog (claim 2), wherein the cytidine analog is decitabine (claims 3, 16, 18-22), wherein the disease associated with the abnormal cell proliferation is a hematological disorder (claim 4), wherein the decitabine inhibitor is administered intravenously (claims 17, 18), wherein the DNA methylation inhibitor is administered prior to the administration of the immuno-modulating agent (claim 23), and a kit for treating a disease associated with abnormal cell proliferation comprising a container that contains decitabine and an immuno-modulating agent (claim 24).

Zaharko et al teach a method for treating leukemia comprising administering decitabine (also known as 5-aza-2'deoxyctidine or DAC) in combination with the immuno-modulating agent pyran copolymer (abstract; page 1255, col. 2; p. 1256, col. 1; Fig. 5). Zaharko et al teach that the pyran was administered the day after decitabine (p. 1256, col. 2; p. 1263, col. 2). Zaharko et al teach the contents of the claimed kit: decitabine and an immuno-modulating agent, pyran copolymer. All of the limitations of the claims are met.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 8-10, 16, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zaharko et al (Cancer Treatment Reports, 1984, 68:1255-1256) in view of Zagodzdon et al (Int J Cancer, 1998, 77:720-727).

The claims are drawn to the method of claim 1 wherein the immuno-modulating agent is an interleukin (claim 8), wherein the interleukin is IL-12 (claims 9, 10), wherein the DNA methylation inhibitor is decitabine and the immuno-modulating agent is IL-12 (claim 16), a kit for treating a disease associated with abnormal cell proliferation comprising a container that contains decitabine and the immuno-modulating agent IL-12 (claim 25).

Zaharko et al teach a method for treating leukemia comprising administering decitabine (also known as 5-aza-2'deoxyctidine or DAC) wherein treatment with decitabine resulted in lengthy increases in survival times (abstract; p. 1256, col. 2 to p. 1257col. 1; Figure 2; Table 1). Zaharko et al does not teach combining decitabine treatment for leukemia with IL-12 treatment.

Zagodzdon et al teach a method of treating leukemia with IL-12 wherein treatment with IL-12 resulted in an increased survival time (Figures 1 and 2). Zagodzdon et al teach that IL-12 stimulates proliferation and cytotoxic activity of natural killer and T-cells and induces secretion of cytokines all of which make it an attractive candidate for tumor immunotherapy (p. 720, col. 1).

These references suggest the importance of each of these agents in leukemia treatment. However, the references are deficient in that they do not teach using these decitabine and IL-12 together. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use decitabine taught by Zaharko et al and IL-12 taught by Zagodzdon et al in combination in order to treat leukemia. One of ordinary skill in the art would have been motivated to use decitabine and IL-12 in combination in a method of treating a disease associated with abnormal cell proliferation or leukemia in view of the importance of eliminating tumor cells and increasing survival time of leukemia patients. Each of these agents had been taught by the prior art to be effective in the treatment of leukemia and increasing survival time of leukemia patients, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima*

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facie obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims and composition claim, given the teaching of the prior art of a method of using either decitabine or IL-12 in the process of treating a disease associated with abnormal cell proliferation or leukemia, it would have been obvious to treat a disease associated with abnormal cell proliferation or leukemia with both decitabine and IL-12 because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for the same purpose of treating a disease associated with abnormal cell proliferation or leukemia. One of ordinary skill in the art would have reasonably expected to obtain effective treating a disease associated with abnormal cell proliferation or leukemia with either or both of these agents since both had been demonstrated in the prior art to successfully treat leukemia.

7. **Conclusion:** No claim is allowed.

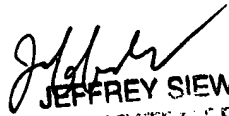
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
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JEFFREY SIEW
SUPERVISORY PATENT EXAMINER